Guidelines in trauma-related bleeding and coagulopathy: an update

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Purpose of review
The diagnosis and treatment of patients with severe traumatic bleeding and subsequent trauma-induced coagulopathy (TIC) is still inconsistent, although the implementation of standardized algorithms/treatment pathways was repeatedly linked to improved outcome. Various evidence-based guidelines for these patients now exist, three of which have recently been updated.

Recent findings
A synopsis of the three recently updated guidelines for diagnosis and treatment of seriously bleeding trauma patients with TIC is presented: (i) AWMF S3 guideline 'Polytrauma/Seriously Injured Patient Treatment' under the auspices of the German Society for Trauma Surgery; (ii) guideline of the European Society of Anesthesiology and Intensive Care (ESAIC) on the management of perioperative bleeding; and (iii) European guideline on the management of major bleeding and coagulopathy after trauma in its 6th edition (EU-Trauma).

Summary
Treatment of trauma-related bleeding begins at the scene with local compression, use of tourniquets and pelvic binders and rapid transport to a certified trauma centre. After arrival at the hospital, measures to record, monitor and support coagulation function should be initiated immediately. Surgical bleeding control is carried out according to 'damage control' principles. Modern coagulation management includes individualized treatment based on target values derived from point-of-care viscoelastic test procedures.

Keywords
bleeding, coagulation disorder, guidelines, trauma, treatment

INTRODUCTION

Uncontrolled bleeding with trauma-induced coagulopathy (TIC) remains - after traumatic brain injury (TBI) – the most common cause of death after severe injury [1▪▪]. Death from bleeding mostly occurs within 4–6 h after injury [2] and is potentially preventable by rapid control of the bleeding source and restoration of haemostasis [3,4▪]. The diagnosis and treatment of these patients is inconsistent [5–7], although in retrospective studies the implementation of standardized algorithms/treatment pathways was repeatedly associated with improved outcome [8,9▪,10]. This paper summarizes current recommendations based upon three recently updated national (German AWMF-S3 guideline [11▪▪,14]) and European guidelines (guideline of the European Society of Anesthesiology and Intensive Care (ESAIC) on the management of perioperative bleeding [12▪▪,15] and the European guideline on the management of major bleeding and coagulopathy after trauma in its 6th edition (EU-Trauma [13▪▪,15]).

PREHOSPITAL PHASE OF CARE

The treatment of seriously injured/bleeding patients begins at the scene in context of a structured emergency medical service (EMS; [16]). This is where PHTLS (Prehospital Trauma Life Support) is used for 'primary survey' with focus on life-threatening conditions [16]. Active bleeding injuries, especially to the extremities thereby compromising vital functions, should be addressed with priority according to the C-ABCDE scheme (AWMF: A [11▪▪]) and, if

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KEY POINTS

- Uncontrolled bleeding with complicating trauma-induced coagulopathy (TIC) remains the most common preventable cause of death in polytrauma.
- Surgical bleeding control and haemostatic therapy are performed according to the up-dated guidelines.
- Treatment of trauma-related bleeding begins at the scene of the accident with compression, tourniquets and a pelvic sling to prevent further blood loss, followed by rapid transport to a certified trauma centre.
- Targeted measures for surgical bleeding control as well as diagnostics, monitoring and support of coagulation function must be initiated in the trauma room immediately after hospital admission.

possible, stopped/controlled immediately (AWMF: GPP [11▪▪]). The aim is to minimize further blood loss/haemorrhagic shock which have been identified as key drivers of TIC due to secondary endotheliopathy and cellular hypoxia [17▪▪]. Active bleeding to the extremities should be addressed by the following step-by-step approach:

(1) Local, manual compression (AWMF: A [11▪▪]; EU: 1B [13▪▪]).
(2) Compression bandage, if possible, with a haemostatic agent (AWMF: A [11▪▪])
(3) Tourniquet (AWMF: A [11▪▪]; EU: 1B [13▪▪])

Avoid further blood loss!

When using tourniquets, adequate analgesia and the timepoint of application must be documented [18]. The time window for safe application of up to two hours was recently confirmed [18]. The use of a pelvic sling/binder is recommended in pelvic ring injury with/without hemodynamic instability (AWMF: GPP [11▪▪]; EU: 1C [13▪▪]). For penetrating wounds with active bleeding, e.g. gunshot, blast and/or stab wounds, or head injuries with active bleeding, direct wound tamponade and/or dressing with chitosan should be applied (AWMF: A for bleeding stab wounds, AWMF: B for gunshot/blast wounds and head injuries [11▪▪]). Chitosan is available as gauze/granules, binds erythrocytes/thrombocytes as a haemostyptic and mediates vasoconstriction independent of coagulation factors [19]. Pneumatic tamponades or simple catheters are suitable for acute oronasopharyngeal bleedings (AWMF: 0 [11▪▪]).

Prehospital ultrasound

For the early detection/exclusion of pneumothorax with/without bleeding (haematothorax/haematopneumothorax), pericardial effusion and/or free intra-abdominal fluid, a prehospital ultrasound examination can be performed if a thoracoabdominal injury is suspected (AWMF: 0 [11▪▪]; EU: 2B [13▪▪]). An unrelieved tension pneumothorax is the most common preventable cause of death prehospital and should be decompressed in case of any suspicion [20▪▪].

Bleeding and coagulation disorders

The prognostically unfavourable 'lethal triad' of hypothermia, acidosis and existing/evolving coagulopathy should already be addressed prehospital by (AWMF: GPP [11▪▪]):

(1) Temperature management aiming for normothermia
(2) Treatment of haemorrhagic shock by rapid control of bleeding, volume management and coagulation therapy
(3) Oxygenation and ventilation/intubation according to intubation criteria.

Since the publication of the landmark CRASH-2 study [21], the use of antifibrinolytic tranexamic acid (TXA) within 3 h of trauma/onset of bleeding is recommended in patients with imminent and/or manifest haemorrhagic shock (AWMF: B [11▪▪]; EU: 1A [13▪▪]). In patients with ongoing and/or uncontrollable bleeding, fibrinogen concentrate may be considered after TXA (AWMF: 0 [11▪▪]). The early administration of both agents in the aforementioned sequence promotes blood clot formation and stability [22] and was associated with survival in retrospective studies [23]. The prehospital provision of blood products (erythrocyte and plasma concentrates including lyophylized plasma) remains under debate in the light of recent studies [24–32] and can be considered for patients with uncontrollable bleeding, provided that appropriate logistics are in place and the administration does not delay transport (AWMF: 0 [11▪▪]). At present, the EU-Trauma guideline refrains from a clear recommendation due to still inconsistent data [13▪▪].

EARLY IN-HOSPITAL DIAGNOSTICS

After admission to the hospital, it remains important to continue all efforts to minimize further blood loss using the aforementioned strategies. The Advanced Trauma Life Support (ATLS) classification of

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haemorrhagic shock is recommended for immediate clinical assessment (EU: 1C [13▪▪]). The inclusion of base excess (BE) has substantially upgraded the classification since its last revision. In addition, the EU-Trauma guideline favours the shock index (SI) as ratio of heart rate to systolic blood pressure over isolated readings (EU: 1C [13▪▪]).

Diagnostic imaging

In patients with blunt and/or penetrating thoracoabdominal injuries, an extended ultrasound examination (eFAST) should be performed in the resuscitation bay (AWMF: B [11▪▪]; EU: 1C [13▪▪]). In haemodynamically unstable patients with chest trauma, pericardial tamponade has to be excluded (AWMF: GPP [11▪▪]). Repeated checks are important even after restoration of adequate circulation/perfusion and in the event of pathological findings during subsequent imaging (AWMF: B [11▪▪]). In the absence of need for immediate intervention/operation and/or resuscitation and if systolic blood pressure is not < 60 mmHg, a contrast-enhanced whole-body CT (WBCT) scan including cranial slicing (CCT) is performed without delay to identify the injury pattern and sources of bleeding/vascular injuries (AWMF: A [11▪▪]; EU: 1B [13▪▪]).

Standard laboratory parameters

Since TIC is recognized as own entity, coagulation diagnostics and therapy should be initiated at latest/immediately upon arrival to the resuscitation bay (AWMF: A [11▪▪]; EU: 1B [13▪▪]). The basic diagnostics include rapid and repeated/serial measurements of

(1) Haemoglobin and/or haematocrit to estimate blood loss including dynamics (EU: 1B [13▪▪]; ESAIC: 1C [12▪▪])
(2) Blood gases (ABG with base deviation and serum lactate) to monitor tissue perfusion/oxygenation and dynamic blood loss/shock depth including treatment monitoring (AWMF: A [11▪▪]; EU: 1B [13▪▪]; ESAIC: 1C [12▪▪])
(3) Standard coagulation tests, e.g. PT time/INR/Quick, aPTT, fibrinogen and platelet count (AWMF: A [11▪▪]; EU: 1C [13▪▪]).

Functional coagulation diagnostics and management

The results from three recent RCTs have called into question the empirical treatment of coagulation dysfunction in severely bleeding trauma patients [25,33,34]. In the PROCOAG trial, blind administration of prothrombin complex concentrate (PCC) was even associated with a higher rate of thromboembolic events [33]. Therefore, all three guidelines promote the use of viscoelastic test procedures as quickly as possible to improve the diagnosis of the underlying disorder and to guide subsequent targeted treatment with blood products and haemostatic agents (AWMF: A [11▪▪]; EU: 1B/1C [13▪▪]; ESAIC: 2C/1C [12▪▪]). While the AWMF guideline recommends the measurement of platelet function (AWMF: B [11▪▪]), its routine determination no longer plays a role in the EU-Trauma guideline; on the contrary, measurement of platelet function should even be avoided due to lack of evidence (EU: 1C [13▪▪]). In patients with a central venous catheter (CVC) in place, the determination of central venous oxygen saturation or the arterio-venous oxygen difference are recommended as surrogate for the oxygen supply:consumption ratio which may identify candidate patients for blood transfusion in an individualized treatment approach (ESAIC: 1C [12▪▪]).

Surgical bleeding control

The time between injury and bleeding/bleeding source control should be kept to minimum (EU: 1B [13▪▪]). Patients with an obvious/proven or suspected active source of bleeding and those in haemorrhagic shock should be referred to immediate intervention/surgery (EU: 1B [13▪▪]). The well established 'damage control' surgery techniques/procedures are still the mainstay (AWMF: B [11▪▪]; EU: 1B [13▪▪]; Table 1). In case of a mechanically unstable pelvic ring along with hemodynamic instability, mechanical closure and stabilization are performed as quickly as possible (AWMF: A [11▪▪]; EU: 1B [13▪▪]). If bleeding persists and/or if timely endovascular bleeding control (i.e. angioembolization) is

Table 1. Trigger factors for the activation of the DCS (modified from [38,39])

• Persistent hemodynamic instability
• Multiple life-threatening/penetrating injuries
• Profound haemorrhagic shock
• Injury severity score (ISS) >35
• Persistent acidosis (pH < 7.2)
• Manifest coagulopathy
• Hypothermia (core body temperature $< 35^{\circ}$C)
• Massive transfusion (>10 EC)
• Necessity of a resuscitation room thoracotomy/laparotomy
• Need for an additional angioembolization
• Mass casualty incident

EC, erythrocyte concentrates.

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not available, temporary extraperitoneal packing is recommended (EU: 1C [13▪▪]); if necessary, this can be combined with open abdominal surgery (EU: 1C [13▪▪]) and this along with topical haemostatics for moderate venous/arterial bleeding from parenchymal organ injuries (EU: 1B [13▪▪]). If hemodynamic instability persists and is refractory due to an intra-abdominal lesion with free fluid, emergency laparotomy is performed (AWMF: B [11▪▪]), preferably as median laparotomy in the acute setting (AWMF: B [11▪▪]).

A clinically relevant and progressive haemothorax should be relieved by a chest drain (AWMF: B [11▪▪]); the same applies to pericardial decompression in case of proven pericardial tamponade with deteriorating vital parameters (AWMF: B [11▪▪]). If an initial blood volume > 1500 ml or 200 ml/h over 2–4 h is observed from the drain, a thoracotomy can be performed in stable/unstable patients (AWMF: GPP [11▪▪]). Emergency thoracotomy should be performed for penetrating thoracic/thoracoabdominal injuries, especially after acute/observed onset of cardiac arrest (AWMF: B/GPP [11▪▪]). If a penetrating thoracic injury is the cause of hemodynamic instability this should be treated with an immediate exploratory thoracotomy (AWMF: A [11▪▪]).

Endovascular procedures and REBOA

Bleeding from parenchymal abdominal organs should be treated endovascularly by means of embolization (AWMF: B [11▪▪]). In case of injuries to spleen and liver with evidence of arterial bleeding, selective angioembolization should be performed over surgery, or alternatively laparotomy, if possible, in patients who are haemodynamically stable or can be stabilized (AWMF: B [11▪▪]). Injuries that do not require immediate intervention should be closely monitored while ensuring coagulation function (AWMF: B [11▪▪]). It is important to recognize and address secondary dynamics with possible two-stage rupture! To gain time to definitive bleeding control, endovascular balloon occlusion of the aorta (REBOA) can be considered in severe and noncompressible trunk bleeding below the diaphragm and in refractory haemorrhagic shock (AWMF: 0 [11▪▪]; EU: 2C [13▪▪]). However, adverse effects must be considered, e.g. severe organ and spinal ischemia, pseudoaneurysms, thromboembolic events and severe reperfusion injury [35]!

Haemostasis therapy

If not already administered prehospital, patients with life-threatening bleeding, haemorrhagic shock and/or relevant risk of bleeding should be given 1 g tranexamic acid (TXA) intravenously over 10 min immediately after admission to the resuscitation bay – but, if possible, within a time window of 3 h after trauma/onset of bleeding - followed by 1 g TXA by infusion over 8 h if necessary (AWMF: A [11▪▪]; EU: 1A [13▪▪]; ESAIC: 1A [12▪▪]). While in the acute phase, administration is also carried out without viscoelastic evidence of hyperfibrinolysis (EU: 1B [13▪▪]), further TXA (bolus) administration should be based on viscoelastic test results with direct evidence of hyperfibrinolysis, especially if therapy is started outside the 3 h time window (AWMF: B [11▪▪]); restrictive administration should be considered if there is viscoelastic evidence of fibrinolytic 'shutdown' (ESAIC: 2C [12▪▪]).

All three guidelines recommend the use of viscoelastic test procedures as quickly as possible to further guide targeted coagulation treatment with blood products and haemostatic agents (AWMF: A [11▪▪]; EU: 1B/1C [13▪▪]; ESAIC: 2C/1C [12▪▪]). In the hyperdynamic bleeding situation, fibrinogen is the first coagulation factor to reach critical levels [36], so that after TXA to reverse any hyperfibrinolysis, rapid and rather liberal substitution should be initiated (initially 3-(4)6 g or 30–60 mg/kg; AWMF: A [11▪▪]; EU: 2C [13▪▪]). The administration of fibrinogen concentrate is indicated in cases of bleeding with hypofibrinogenemia and accompanying viscoelastic signs of functional fibrinogen deficiency or a fibrinogen level ≤1.5 g/l according to the Clauss method (EU: 1C [13▪▪]; ESAIC: 1B [12▪▪]). If critical bleeding persists and as a component of targeted coagulation therapy – after normalization of fibrin polymerization (EU: 2C [13▪▪]) – prothrombin complex concentrate (PPSB) should be administered based upon viscoelastic evidenced delayed clot initiation/deficiency of clotting factors (AWMF: B [11▪▪]; EU: 2C [13▪▪]; ESAIC: 1B [12▪▪]). Monitoring and, if necessary, substitution of FXIII in the event of persistent bleeding should be part of a comprehensive and goal-oriented treatment algorithm (EU: 2C [13▪▪]; ESAIC: 2C [12▪▪]). In massive transfusion, hypocalcemia < 0.9 mol/l should be avoided and normocalcemia should be the target (AWMF: B [11▪▪]; EU: 1C [13▪▪]; ESAIC: G2 [12▪▪]).

Administration of blood products

The indication for the transfusion of blood products should be determined individually based upon clinical criteria, extent of injury and blood loss, circulation and oxygenation (AWMF: B [11▪▪]). It is agreed that normovolemia with a haemoglobin of 7–9 g/dl should be the target (AWMF: B [11▪▪]; EU: 1C [13▪▪]; ESAIC: 1B [12▪▪]). If plasma volume needs to be replaced in massive bleeding, therapeutic

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plasma should be used as early as possible (AWMF: B [11▪▪]). If massive bleeding/transfusion is expected, there are two alternatives (EU: 1C [13▪▪]):

(1) Fibrinogen concentrate and packed red blood cell concentrates (pRBCs)
(2) Fresh frozen plasma concentrates (FFP) in ratio FFP:pRBCs of at least 1 : 2 (EU: 1C [13▪▪]) or FFP: pRBC:platelets of 4 : 4:1 (AWMF: B [11▪▪]).

Otherwise, the administration of therapeutic plasma should be restrictive (AWMF: B [11▪▪]; ESAIC: G3 [12▪▪]) and should neither be used to correct hypofibrinogenemia - if concentrates are available (EU: 1C [13▪▪]) – nor for volume replacement (ESAIC: G3 [12▪▪]). When implementing an FFP-based strategy, it is recommended to use laboratory coagulation parameters/tests to guide further administration, e.g. PT and/or APTT >1.5× reference and/or viscoelastic indicators for coagulation factor deficiency (EU: 1C [13▪▪]). As the coagulation process occurs on the surface of activated platelets, the platelet count should be $>50 \times 10^9$/l in patients with ongoing bleeding and $>100 \times 10^9$/l in patients with either TBI and/or spinal injury (EU: 2C [13▪▪]). In a ratio-based coagulation concept, attention should be given to a high platelet-pRBC ratio (AWMF: B [11▪▪]). The intra- and postoperative use of a cell saver can be considered (EU: 2B [13▪▪]; ESAIC: 2B [12▪▪]).

Tissue oxygenation, blood pressure and volume therapy

In haemorrhagic shock, volume therapy should be initiated in a reduced form following the 'permissive hypotension'-concept until surgical haemostasis is achieved to keep the circulation low stable and not further increase bleeding/blood loss (AWMF: B [11▪▪]; EU: 1B [13▪▪]). A mean arterial pressure (MAP) of 65 mmHg (RR_{syst} 80 mmHg) is targeted in patients without TBI and without preexisting cardiopulmonary diseases during the pre, intra- and early postoperative phase (3–6 h) and a systolic blood pressure (RR_{syst}) of ≥90/110 mmHg in patients with suspected isolated/leading TBI (AWMF: B/A [11▪▪]). In case of haemorrhagic shock, TBI (GCS < 9) and/or spinal cord injury with neurological symptoms, a MAP of 85 mmHg should be aimed for (AWMF: B [11▪▪]). Even single drops in arterial oxygen saturation < 90% should be avoided (AWMF: A [11▪▪]). If the target blood pressure cannot be achieved by fluids alone, titrated vasopressors can be considered (AWMF: GPP [11▪▪]; EU: 1C for noradrenaline [13▪▪]). Balanced, isotonic crystalloid solutions are preferred, ideally prewarmed (AWMF: A [11▪▪]; EU: 1B [13▪▪]; ESAIC: 1B [12▪▪]).

Optimization of the environment

Already prehospital it is mandatory to prevent the 'lethal triad' by maintaining body temperature and providing adequate resuscitation, oxygenation and ventilation (AWMF: GPP/B [11▪▪]; EU: 1C [13▪▪]; ESAIC: G2 [12▪▪]). A general rule promotes that a drop in temperature by 1°C leads to a 4–10% reduction in coagulation factor activity [37]. Correction of preexisting acidosis should be considered, although pH correction alone does not directly reverse acidosis-induced impairment of coagulation function (ESAIC: G2 [12▪▪]). Figure 1 provides a summary of modern coagulation management in trauma.

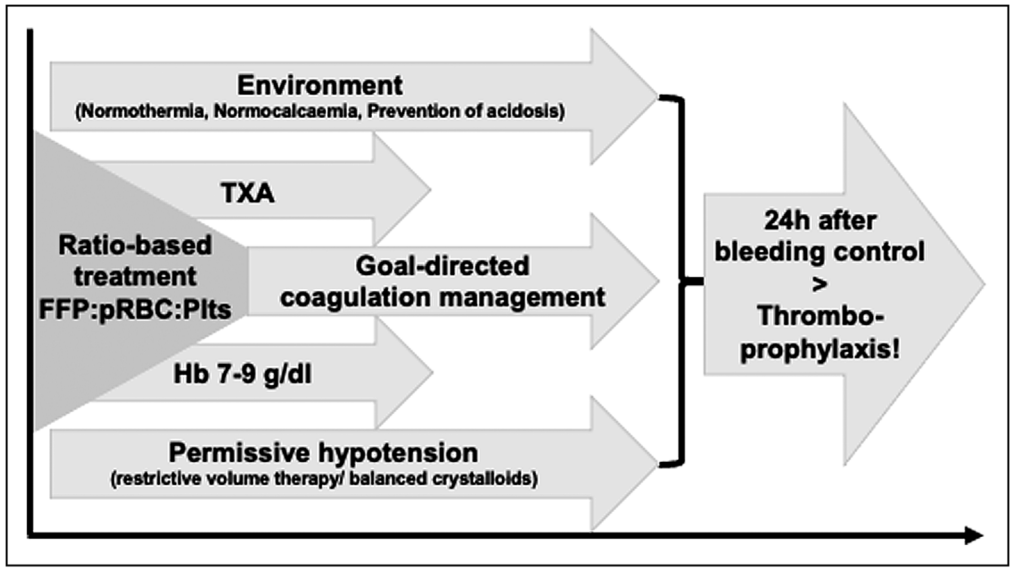

FIGURE 1. Expemplar 'hybrid'-concept of modern coagulation management in severely injured and bleeding patients.

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CONCLUSION

Three up-dated guidelines provide evidence-based guidance on how to treat severely injured and bleeding trauma patients with TIC.

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